Multi-scale modeling for prediction of distributed cellular properties in response to substrate spatial gradients in a continuously run microreactor

Lencastre Fernandes, Rita; Krühne, Ulrich; Nopens, Ingmar; Jensen, Anker Degn; Gernaey, Krist

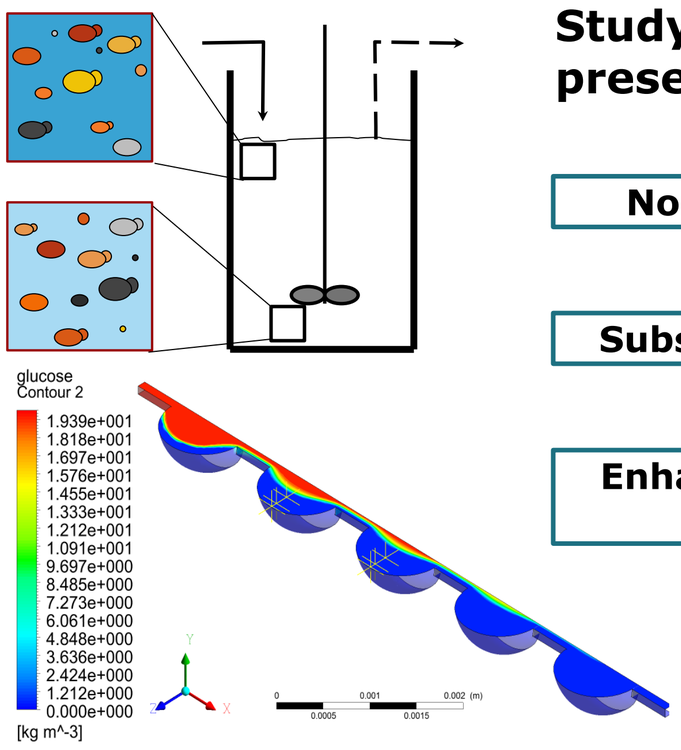
Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

Multi-scale modelling for prediction of distributed cellular properties

R. Lencastre Fernandes[1], U. Krühne[1], I. Nopens[2], A. D. Jensen[3], K. V. Gernaey[1]

[1] PROCESS - Dept. of Chemical and Biochemical Engineering, Technical University of Denmark
[2] BIOMATH- Dept. of Mathematical Modelling, Statistics and Bioinformatics, Ghent University
[3] CHEC - Dept. of Chemical and Biochemical Engineering, Technical University of Denmark



Studying the development of cell property distributions in the presence of spatial substrate gradients

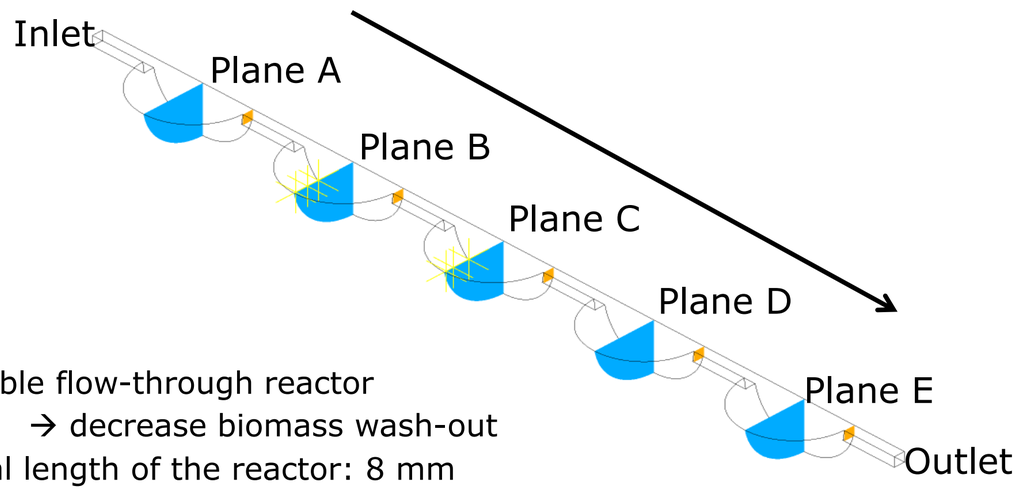
Non-ideal mixing → **Substrate gradients** → **Enhance cell-to-cell variability**

Reactor Hydrodynamics ↔ **Bulk composition** ↔ **Distributions of Cell Properties**

Computational Fluid Dynamics (CFD) ↔ **Unstructured Model (UM)** ↔ **Population Balance Model (PBM)**

Flow velocities Streamlines ↔ **Local concentrations of Glucose, Ethanol and Total Biomass** ↔ **Local distributions of cell size and cell cycle position**

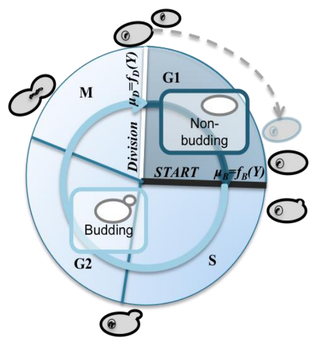
Case study: Microbioreactor



- Bubble flow-through reactor
  → decrease biomass wash-out
- Total length of the reactor: 8 mm
- Anaerobic growth of budding yeast
- Slow feed of glucose: 1 nl/s vs. 0.1 nL/s
- Laminar flow
- Incompressible fluids
- Diffusion is *not* taken into account

- Implemented in CFX 12.1 and the biological model was implemented using CEL language
- Hexaedral mesh with 32159 elements and 36535 nodes
- PBM discritized in 2x 20 pivots using the fixed-pivot method

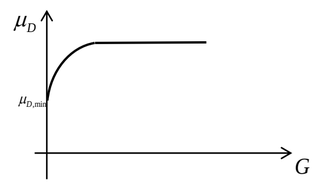
2-stage cell size structured PBM...



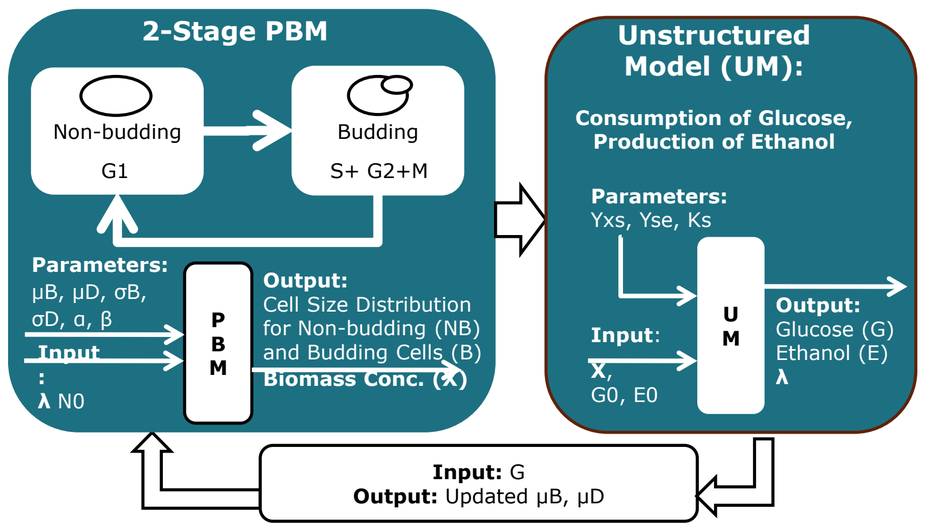
Critical Budding and Division Sizes as functions of the substrate concentration

$$\mu_B = k_B \frac{G}{G + K_{BG}} + \mu_{B,\min}$$

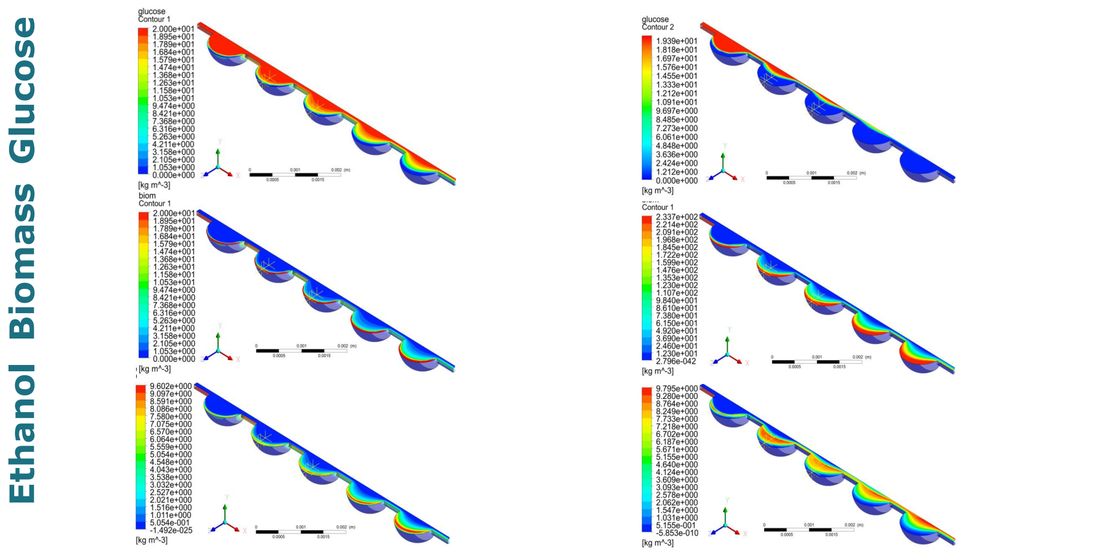
$$\mu_D = k_D \frac{G}{G + K_{DG}} + \mu_{D,\min}$$



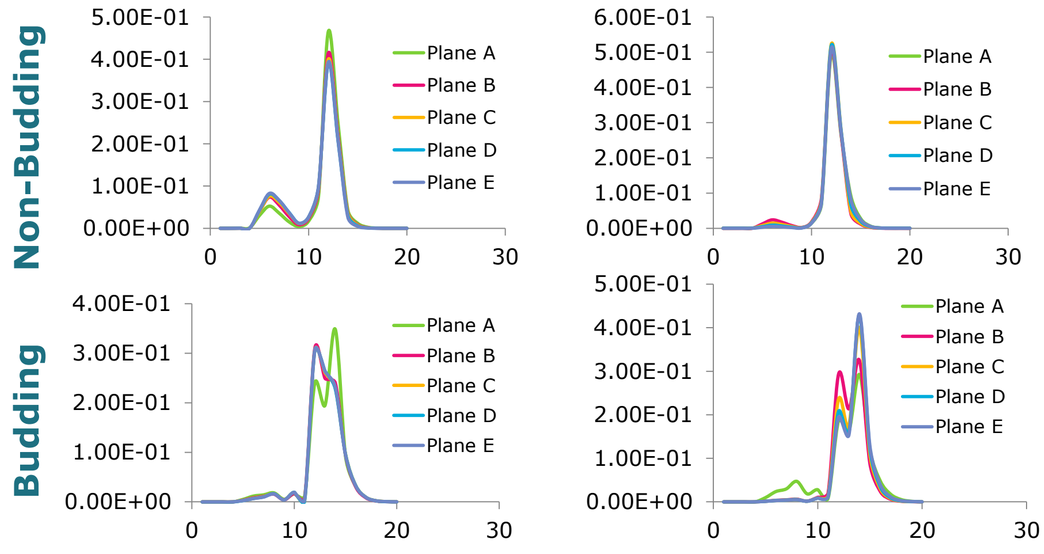
... coupled to an unstructured model



Concentration profiles



Local Concentrations and distributions



Conclusion & Outlook

- Challenge in understanding the local distributions as they result from the interplay of flow and the population dynamics
- Proof-of-concept of integration of a CFD and PBM for multi-scale biological applications.
- *In silico* simulation of various scenarios: different flow conditions, cellular kinetics, etc.
- Experimental Validation: overall distribution of biomass, bulk concentrations and cell distributions at the outlet

Rita Lencastre Fernandes
Center for Process Engineering and Technology
Dept. Chemical and Biochemical Engineering
Technical University of Denmark
rlf@kt.dtu.dk

Acknowledgments
Danish Council for Strategic Research (Project no. 09-065160) and ERA-Net Industrial Biotechnology (Project no. EIB.08.031) are acknowledged for the financial support.

PROCESS
Center for Process Engineering and Technology